

## REMARKS

### A. Status of the Claims

Claims 17-36 are pending and under examination.

### B. The Filipcik Declaration

Along with the response filed on August 14, 2008, Applicants provided the a third declaration from Dr. Filipcik. Applicants stated in the response that although the declaration was unsigned, it had been approved by Dr. Filipcik and the signed declaration would be forwarded to the Office in due course. The final Office Action acknowledged receipt of the unsigned declaration, but noted that Applicants had not yet submitted the signed declaration. Applicants would like to thank the Examiner for bringing this to their attention. The signed declaration is being submitted along with this response. Applicants respectfully request reconsideration of this case in view of the evidence provided in the third Filipcik Declaration.

### C. Objections to the Drawings and Specification

Beginning on the last line of page 16 of the Action, the Examiner objects to the drawings and the drawings and the specification. The Examiner refers to new matter contained in the amendment filed August 14, 2008. These objections were made in error because no amendments were made to the specification or drawings on August 14, 2008. This error was confirmed by a telephone call to Examiner Leavitt on December 23, 2008. Applicants, therefore, request the withdrawal of these objections.

### D. Objection to the Claims

The Action objected to claims 17-37 because the recitation "the molecules have truncated at least 30 nucleotides downstream of the start codon and truncated at least the 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence" in claims 17 and 37 because it is allegedly unclear. Applicants disagree. It is unclear why the Examiner finds this unclear, but

Applicants will point out that the recitation says “have truncated” not “has a truncation,” as it appears the Examiner’s reasoning is based on the latter. Applicants, therefore, request the reconsideration and withdrawal of this objection.

It is further noted, that Examiner does not find the language of the current claims unpatentable. As stated in § 706.01, “[t]he refusal to grant claims because the subject matter as claimed is considered unpatentable is called a ‘rejection.’ The term ‘rejected’ must be applied to such claims in the examiner’s action. If the form of the claim (as distinguished from its substance) is improper, an ‘objection’ is made.”

#### **E. The Claims are Enabled**

Claims 17-33 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Action indicates that the specification is enabling for claims directed to a transgenic rat whose genome comprises a transgene comprising a DNA construct encoding a N- and C-terminally truncated human tau protein of SEQ ID NO: 9, said DNA operably linked to a promoter, wherein the promoter is a mouse Thy-1 promoter, wherein said truncated tau protein is expressed in the rat brain and neurofibrillary pathology occurs in the rat when compared to normal rats. The Action asserts, however, that there is insufficient description to enable the full scope of the current claims. Applicants traverse this rejection.

The Action appears to focus on the following three areas in the enablement rejection: (1) the scope of the transgenic non-human animal enabled by the specification; (2) the scope of the cDNA molecule coding for N- and C- terminally truncated tau molecules enabled by the specification; and (3) the scope of the promoter enabled by the specification. Applicants address each of these areas below.

## **1. The Transgenic Non-Human Animal**

The Action asserts that the specification is not enabled for any transgenic animal other than rat because transgene expression in different species of transgenic animals is not predictable and varies according to the particular host species, specific promoter/gene combinations, random transgene insertion, and genetic imprinting. The Action cites publications by Williams (2000), Moreadith (1997), Keefer (2004), and Sigmund (2000) as allegedly supporting this rejection. Applicants traverse.

### **(a) The Specification Provides an Enabling Disclosure of How to Make and Use a Transgenic Non-Human Animal**

The present specification teaches how to make and use non-human transgenic animals that exhibit pathology that is a useful model for Alzheimer's disease. This is demonstrated through working examples describing the generation and study of transgenic rat line #318. Fig. 10 and the accompanying descriptions on pages 20-21 and 25 of the present specification depict a comparison of neurofibrillary pathology in the brains of patients suffering from Alzheimer's disease and those observed in the brain of transgenic rat line #318. Equivalent pathological structures were observed when comparing the two samples (*Id.*; *see also* Figs. 6-8 and their accompanying descriptions at pp 19-20). Neurofibrillary pathology is the most important and earliest immunohistochemical finding in Alzheimer's disease (*see* Braak *et al.*, *Acta Neuropathol* (Berl), 112(4):389-404 (2006)). Accordingly, a transgenic animal that exhibits neurofibrillary pathology is a useful model for Alzheimer's disease.

Moreover, neurofibrillary pathology is not the only Alzheimer's disease related characteristic of the transgenic rats disclosed in the present specification. As described in the declaration of Dr. Filipcik provided with Applicants' response filed on January 10, 2007, the expression of truncated tau in rats is a net inducer of oxidative stress, which is another

pronounced symptom in human Alzheimer's disease (*see* para. 11 of Dr. Filipcik's declaration filed on January 10, 2007). This is further confirmed in a paper by Cente *et al.* (Eur J Neurosci., 24(4):1085-90 (2006)), which discloses that truncated tau induces oxidative stress. Additionally, transgenic rat line #318 exhibits hypertension – up to 220 mm/Hg (Filipcik Declaration, para. 11). It is also easy to induce diabetes in transgenic rat line #318 by using a specific diet formulation (Filipcik Declaration, para. 11). Thus, the transgenic animals encompassed by the current claims are useful models of Alzheimer's disease because they exhibit the most important and earliest immunohistochemical finding in Alzheimer's disease (*i.e.*, neurofibrillary pathology) and they exhibit other pathological features associated with Alzheimer's disease including cognitive impairment, oxidative stress, hypertension, and diabetes (Filipcik Declaration, para. 11).

An additional transgenic rat line, line #24, which contains a cDNA coding for human tau protein that is shorter by 93 nucleotides (31 amino acids) than the cDNA coding for human tau protein in transgenic rat line #318, was described in a second Filipcik Declaration filed on September 17, 2007. The DNA construct used in generating transgenic rat line #24 encodes a protein, which has neurofibrillary pathology producing activity when expressed in brain cells of animals, as evidenced by the fact that transgenic rat line #24 exhibits neurofibrillary pathology. In particular, transgenic rat line #24 developed neurofibrillary lesions in the brain stem, spinal cord, primary motor cortex, and hippocampus (2<sup>nd</sup> Filipcik Declaration, para. 5). Neurological examinations showed similar features in both the #24 and #318 transgenic rat lines. For example, the onset and progression of sensory-motor impairment of animals from transgenic line #318 and transgenic line #24 is almost identical (2<sup>nd</sup> Filipcik Declaration, para. 8). Transgenic

rats from line #24 were also shown to suffer from early cognitive impairment in an object recognition test (2<sup>nd</sup> Filipcik Declaration, para. 8).

The Examiner argued that because transgenic rat line #24 was not disclosed in the specification, it is post-filing art that cannot be relied upon to demonstrate possession of the claimed invention. This is incorrect. An applicant can submit post-filing evidence demonstrating that the application was enabling at the time of filing. MPEP § 2164.05(b). Transgenic rat line #24 was made by the same technique as described in the specification for generating Tg line #318 and using a construction comprising SEQ ID NO: 9 as disclosed in the specification. Thus, the Filipcik Declaration demonstrated that one could make and use an embodiment of the claimed invention by following the description in the specification.

Applicants submitted an approved, but unsigned, third Filipcik Declaration on August 14, 2008. The signed third Filipcik Declaration is being submitted with this response. The third Filipcik Declaration describes yet another transgenic rat line, line #72, as well as studies showing that phenotype resulting from transgenic truncated tau expression was not dependent on genetic background. The same construct as used in the generation of transgenic rat line #318 also was used in the generation of transgenic rat line #72 (3<sup>rd</sup> Filipcik Declaration, para. 5). The onset and progression of neurodegeneration is the same in all three transgenic rat lines (*i.e.* Tg lines #24, #72, and #318) (3<sup>rd</sup> Filipcik Declaration, para. 6). The only observed difference has been that the life span of those animals containing 4 repeat tau (*e.g.* Tg line #72) is much shorter when compared to those animals containing 3 repeat tau region (*e.g.* Tg line #24) of human tau protein (3<sup>rd</sup> Filipcik Declaration, para. 6).

The phenotype produced by transgenic truncated tau expression was not dependent on genetic background (3<sup>rd</sup> Filipcik Declaration, para. 12). The transgene was transferred from the

genetic background of the hypertensive SHR strain (Tg line #72) into the normotensive Wistar strain (WKY) (3<sup>rd</sup> Filipcik Declaration, para. 12). In this new genetic environment, an almost identical phenotype at the level of biochemical examination and behavioral measurements was observed (3<sup>rd</sup> Filipcik Declaration, para. 12 and Figures 6 and 7).

Furthermore, transgenic rats were created that contained both 4-repeat and 3-repeat human truncated tau. The resulting phenotype in transgenic line SHR24/72 (expressing both 3R and 4R truncated tau proteins) was synergistic (3<sup>rd</sup> Filipcik Declaration, para. 13). For example, sensorimotor functions measured by beam walking test were significantly more impaired in transgenic line SHR24/72 (expressing both 3R and 4R truncated tau proteins) when compared with transgenic lines SHR24 (expressing 3R truncated tau) and SHR72 (expressing 4R truncated tau) (3<sup>rd</sup> Filipcik Declaration, para. 13 and Figure 8). In addition, neuroscale evaluation showed that the complete neurobehavioral phenotype was significantly more impaired in transgenic line SHR24/72 (expressing both 3R and 4R truncated tau proteins) when compared with transgenic lines SHR24 (expressing 3R truncated tau) and SHR72 (expressing 4R truncated tau) (3<sup>rd</sup> Filipcik Declaration, para. 13 and Figure 9).

Transgenic rat lines #318, #72 (SHR and WKY genetic backgrounds), and #24 are, therefore, evidence of a transgenic non-human animals having germ and/or somatic cells which comprise a DNA construct comprising a cDNA molecule coding for N- and C-terminally truncated tau molecules, wherein: (1) the cDNA molecule is truncated at least 30 nucleotides downstream of the start codon and truncated at least the 30 nucleotides upstream of the stop codon of the full-length tau cDNA sequence coding for 4-repeat and 3-repeat tau protein; (2) the cDNA molecule comprises SEQ ID No. 9; and (3) the DNA construct encodes a protein, which has neurofibrillary (NF) pathology producing activity when expressed in brain cells. Moreover,

these transgenic animals show that a reproducible phenotype can be achieved from different insertional events and different animal strains.

In addition to rats, a variety of animal models would be suitable Alzheimer's disease (AD) models since AD associated neurofibrillary (NF) pathology, based on paired helical filaments (PHF), occurs in a number of animals. For example, Hartig *et al.* (European Journal of Neuroscience, Vol. 25, pp. 69–80, 2007) shows that PHF-like tau occurs in hamsters, which parallels the situation in AD (abstract). Hartig also notes that PHF-like tau was observed in ground squirrels (p. 69, right col., para. 2).

Huang *et al.*, (Brain Research 771, 1997, 213–220) describes neurofibrillary tangles based on abnormal tau in rabbits. The proteins have a molecular structure that closely resembles that of primates, thus making such an animal system of relevance for human neurodegenerative disease like AD (abstract, p. 214, left col., para. 2, p. 219, left col., para. 2).

Gotz (Brain Research Reviews 35 (2001) 266–286) describes the use of murine models expressing tau as system for the dysfunction of tau and neurodegeneration and dementia based on neurofibrillary lesions (abstract, p. 275, right col., item 4.3). In addition, Lewis *et al.*, (Nat Genet. 2000 Aug; 25(4):402-5)) describes the formation of AD related NF tangles through expression of mutant human tau in mice (abstract). These reference demonstrate that a variety of animals are capable of exhibiting NF pathology and, therefore, are suitable for the study of NF pathology and Alzheimer's disease.

In view of the above, the claims are enabled for non-human transgenic animals and the evidence demonstrates that such animals exhibit characteristics that make them suitable models for Alzheimer's disease.

**(b) The References Cited in the Action**

It is well settled that in examining a patent application, the PTO is required to assume that the specification complies with the enablement provisions of 35 U.S.C. § 112 unless it has acceptable evidence or reasoning to suggest otherwise. MPEP § 2164.04. The Action's evidence and reasoning, however, fail to show that the specification is not in compliance with the enablement provisions of 35 U.S.C. § 112.

First, the Action alleges that Williams (2000) is evidence that transgene expression in different species of transgenic animals is not predictable (Action, p. 4). Williams points out some potential limitations of transgenic animal experiments (Williams, p. 1124, col. 1 to 1126, col. 1). These potential limitations include variability in transgene expression level resulting from differences in gene dosage and the sequences surrounding the insertion site, genetic imprinting, and variability in phenotypes between strains. These limitations, however, are known to those in the art. For example, Williams states that the “conventional practice to deal with [variable expression] is to establish and analyze multiple lines of transgenic mice bearing any specific transgene, each of which represents a different chromosomal event. It is mandatory for most purposed to assess at least two independent lines.” (Williams, p. 1124, col. 2, 3<sup>rd</sup> paragraph). Williams further teaches that “[i]t is a good practice to assess the effects of transgenes or knockouts in more than one mouse strain.” (Williams, p. 1125, col. 1, 3<sup>rd</sup> paragraph). Thus, it is routine in the art to take measures to account for potential variability in transgenic animals. As described in the preceding section, Applicants have confirmed the phenotype of the transgenic rats with multiple lines and in different rat strains.

Next, the Action misstates the teachings of Moreadith (1997). Moreadith discusses the history of the development of stem cell technology and methods employed to create knock-out



mice. Moreadith does not teach that this technology is limited to mice as alleged in the Action. Rather, Moreadith merely stated that this particular technology had not yet been applied to hamster, pig, sheep, cattle, rabbit, rat, mink, monkey, and humans (Summary, p. 214). Moreadith noted that as of 1997, putative pluripotent ES cell lines had been derived from each of these species and, therefore, concluded that it seemed likely that the technology would be advanced into these additional species over the next few years (Summary, p. 14).

Also in regard to Moreadith, it is important to note that this reference is discussing a particular stem cell technology, but the presently claimed invention is not limited to the use of stem cells. For instance, in Example 2 of the application, the employed technique was micro-injecting DNA into fertilized oocytes (not ES cells), which were afterwards implanted to the foster mother in 1 or 2-cell stage and which develop normally into the whole animal. Accordingly, any argumentation that ES cells from different organisms may have different features and might in certain cases not continue developing during embryogenesis does not mean that one could not make and use the claimed invention because the claimed invention is not limited to transgenic animals created from ES cells.

Finally, Moreadith specifically states that “[t]he development of transgenic technology, whereby genes (or mutations) can be stably introduced into the germline of experimental mammals, now allows investigators to create mice of virtually any genotype and to assess the consequences of these mutations in the context of a developing and intact mammal.” (Moreadith (1997), Abstract) (emphasis added). In light of this statement on the state of the art, it is unclear on what grounds the Examiner is basing the argument that the current claims are not enabled with respect to transgenic mice.

The Action cites Keefer (2004) as teaching the inefficiency of pronuclear microinjection and the unpredictability of transgene expression (Action, p. 4-5). Inefficiency and unpredictability, however, are different. Something can be inefficient and predictable. In fact, it is clear that while pronuclear transfer in cattle, sheep, and goats may be inefficient, Keefer finds it predictable to the point that Keefer teaches specific numbers of oocytes from each animal (1000, 300, and 200, respectively) that should be injected to produce 1 founder transgenic animal (Keefer, p. 6-7). “The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art.” *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The state of pronuclear injection as described in Keefer is such that it is routine to inject a few hundred to a thousand oocytes, depending on the animal, to produce a founder transgenic animal. Thus, this is considered reasonable in the field.

Keefer does not appear to show any concern as to whether the transgenic animal will express the desired protein, only a concern as to whether the animal will express high amounts of the protein (Keefer, p. 6-7). In this regard, it is important to note that Keefer is focused on the production of bioproducts in livestock, and not on creating an animal model of a disease. In addition, the primary concerns raised by Keefer with respect the production of transgenic livestock appear to be the long generation intervals and the costs associated with maintaining livestock herds due to the larger size of the animals (Keefer, p. 6). This does not indicate that it will require undue experimentation to make transgenic livestock such as cattle, it only indicates that will take longer and be more expensive when compared to smaller animals like mice because of the longer generation intervals and the increased cost of maintaining larger animals.

Finally, the Action cites Sigmund as corroborating the lack of predictability of phenotypes in transgenic models by disclosing that the phenotype caused by a specific genetic modification is strongly influenced by genes unlinked to the targeted locus (Action, p. 5). While Sigmund describes that the phenotype caused by a specific genetic modification is influenced by other genes, Sigmund's point is that researchers need to use an appropriate control animal when assessing the phenotype of the transgenic animal. In this regard, Sigmund states that it is "the responsibility of the investigator to use common sense and design the best possible control experiments that fit the individual situation, to assess whether the phenotype observed in their model is due specifically to the targeted modification or is affected by other loci." (Sigmund, p. 1428, col. 1, 3<sup>rd</sup> paragraph). Thus, as discussed above with regard to Williams, this variability is a potential limitation of transgenic animals that is known to those in the art. As discussed by both Williams and Sigmund, it is routine in the art to take measures to account for potential variability in transgenic animals. As discussed above, Applicants have confirmed the phenotype of the transgenic rats with multiple lines and in different rat strains.

## **2. The cDNA Molecule Coding for N- and C-Terminally Truncated Tau Molecules**

The Action asserts that the specification is only enabling for a DNA construct encoding a N- and C-terminally truncated human tau protein of SEQ ID NO: 9. Applicants traverse.

It appears that the Examiner's rationale in wanting to limit the claims to only the sequence used in transgenic rat line #318. The sequence in the construct in transgenic rat line #318 comprises SEQ ID NOs: 3, 6, 7, 8, and 9. SEQ ID NO: 9, which is recited in the current claims, encodes the minimally truncated tau protein, which corresponds to nucleotides 741-930 (Specification, FIG. 1). In addition, the inventors have developed transgenic rat line #24, which contains a cDNA coding for human tau protein that is shorter by 93 nucleotides (31 amino acids)

than the cDNA coding for human tau protein in transgenic rat line #318. The sequence used for transgenic rat line #24 corresponds to SEQ ID NO: 12 in the specification. SEQ ID NO: 12 was isolated from tau isotype 44, whereas SEQ ID NO: 9 was isolated from tau isotype 43 (*see* Specification, FIG. 1). Accordingly, the numbering of the nucleotide sequences in SEQ ID NOs: 9 and 12 is somewhat different. SEQ ID NO: 12 comprises SEQ ID NO:9 as shown in the specification where the sequence of SEQ ID NO: 9 can be found in the sequence for SEQ ID NO: 12 at page 10 of the specification beginning at the 15<sup>th</sup> nucleotide in the 7<sup>th</sup> line of SEQ ID NO: 12 and ending at the 22<sup>nd</sup> nucleotide on the 1<sup>st</sup> line of page 11. Thus, the truncated tau cDNA molecule used to generate rat line #24 is encompassed by the current claims as it is truncated at least 30 nucleotides downstream of the start codon and truncated at least the 30 nucleotides upstream of the stop codon of the full-length tau cDNA sequence coding for 4-repeat and 3-repeat tau protein; and the truncated tau cDNA molecule comprises SEQ ID NO: 9 (nucleotides 741-930). The presence of the minimally truncated tau core (SEQ ID No: 9) lacking the N- and C- termini leads to its conformational change, toxic gain of function and the development of the unnaturally tau related NF pathology. The significance of the truncated tau core is demonstrated by the constructs used in the generation of transgenic rat lines #24, #72, and #318. Current claim 17 specifically states that “the cDNA molecule comprises SEQ ID No. 9.”

The scope of the cDNA molecule coding for N- and C-terminally truncated tau molecules encompassed by the claims is enabled at least by the direction provide in the specification and the existence of working examples.

### **3. Promoters**

With respect to promoters, the Action asserts that the specification is enabling only for a mouse Thy-1 promoter. In other words, the Action is asserting that it would require undue

experimentation for a person of ordinary skill in the art to make and use a DNA construct with any promoter other than a mouse Thy-1 promoter. Applicants traverse.

The Examiner's arguments regarding promoters appear to focus on two issues. One being that it was well known at the time of filing that expression of a gene of interest in a transgenic animal requires operable linkage of the gene to a promoter, but current claim 17 does not expressly recite a promoter. The other being that it was also well known in the art that not all promoters result in efficient expression in the appropriate target tissue to result in a useful phenotype. The Examiner's reasoning on both points is inconsistent with the legal standard for enablement.

Enablement must be evaluated from the position of a person of ordinary skill in the art. Moreover, "a patent need not teach, and preferably omits, what is well known in the art." *Hybridtech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1987). The Examiner admits that it was well known at the time of filing that expression of a gene of interest in a transgenic animal requires operable linkage of the gene to a promoter, and that it was also well known in the art that not all promoters result in efficient expression in the appropriate target tissue. Given that the Examiner finds that such things were so well known, why wouldn't a person of ordinary skill in the art be able to make and use them?

The Examiner's argument that expression of a gene of interest in a transgenic animal requires operable linkage of the gene to a promoter is further unavailing because claim 17 does not recite a promoter and does not need to. Expression of a gene of interest in a transgenic animal requires many well-known things including, for example, numerous components for transcription and translation of the gene. Patent claims set forth the limitations of a claimed invention. It is not the purpose of patent claims to describe all of these other elements. In

addition, the specification teaches that a “construct” is a recombinant nucleic acid sequence, generally recombinant DNA sequences, operably linked to tissue specific or general promoter, that is generated for the purpose of the expression of a specific nucleotide sequence(s) in mammalian cells, or is to be used in the construction of other recombinant nucleotide sequences (Specification, p. 6). Thus, in light of the specification, a person of ordinary skill in the art would understand that a “DNA construct” as recited in claim 17 contains a promoter operably linked to the cDNA molecule coding for N- and C- terminally truncated tau molecules.

The Examiner’s argument that not all promoters result in efficient expression in the appropriate target tissue is also unavailing. Numerous promoters were known and readily available to those in the art at the time of the filing of the present application. A person of ordinary skill in the art would further understand that the promoter in the DNA construct is a promoter suitable for expression in mammalian cells. The specification further teaches methods for the preparation and evaluation of DNA constructs that may be used in the presently claimed invention (Specification, p. 12, ln. 12-38). With regard to promoters for eukaryotic expression, this passage teaches the use of appropriate promoters for brain expression or ubiquitous expression. Additional disclosure of cloning truncated tau coding by incorporating appropriate restriction sequences so that it can be cloned under general or tissue specific promoters in an eukaryotic expression vector is disclosed in the specification at page 21, lines 8-36. As noted in the specification, these methods are described in Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (Cold Spring Harbor Laboratory Press, 1989) (Specification, p. 21, ln. 34-36).

As mentioned above, numerous promoters are known and readily available to those in the art. Examples of some promoters that have been used to drive transgene expression in the

central nervous system of various mammals are provided in the review article by Fitzsimons *et al* (Methods 28:227–236 (2002); *see e.g.*, Tables 1 and 2). The cytomegalovirus (CMV) promoter, for example, had been used to drive the expression of several different transgenes in the central nervous system of rat, mice, and monkeys (Fitzsimons, Table 1). In addition, the publication by Lewis *et al.* (Nat Genet. 25(4):402-5 (2000)) shows the expression of human tau protein in mice using the mouse prior promoter (MoPrP).

It would require only routine cloning procedures, such as those described in the present specification or in Sambrook *et al.*, to place a cDNA molecule coding for N- and C-terminally truncated tau molecules under the control of an appropriate promoter. Such routine cloning does not constitute undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Accordingly, the scope of promoters encompassed by the current claims is enabled by the specification.

#### **5. Claim 37**

It is the Examiner's burden to substantiate a rejection based on a lack of enablement. The Examiner, however, does not provide any specific reasons for rejecting independent claim 37. Most of the Examiner's arguments are not applicable to claim 37. Applicants, therefore, request that the Examiner withdrawal this rejection or set forth a basis for its rejection so Applicants can have an opportunity to respond.

#### **6. Summary**

To be enabling within the meaning of 35 U.S.C. § 112, the application must contain a description sufficient to enable one skilled in the art to make and use the claimed invention without unduly extensive experimentation. For the reasons set forth above, the present

specification satisfies this requirement. Applicants, therefore, request the withdrawal of this rejection.

The Examiner is invited to contact the undersigned attorney with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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